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     (FILE 'HOME' ENTERED AT 18:02:24 ON 22 MAR 2006)

     FILE 'CAPLUS, MEDLINE' ENTERED AT 18:02:34 ON 22 MAR 2006
L1             0 S EPOTHILONE? (P) ETHANOL (P) POLYOXYETHYLENE SORBITAN ?OLEATE
L2             0 S EPOTHILONE? (P) POLYOXYETHYLENE SORBITAN ?OLEATE (P) CYCLODEX
L3             0 S EPOTHILONE? (P) POLYOXYETHYLENE SORBITAN ?OLEATE
L4             0 S EPOTHILONE? (P) POLYOXYETHYLENE SORBITAN (P) CYCLODEXTRIN?
L5             7 S EPOTHILONE? (P) CYCLODEXTRIN?
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L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:549398 CAPLUS
DOCUMENT NUMBER: 131:169392
TITLE: Fermentative preparation process for cytostatics and crystal forms thereof
INVENTOR(S): Hofmann, Hans; Mahnke, Marion; Memmert, Klaus; Petersen, Frank; Schupp, Thomas; Kusters, Ernst; Mutz, Michael
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9942602	A2	19990826	WO 1999-EP1025	19990217
WO 9942602	A3	19991125		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6194181	B1	20010227	US 1999-248910	19990212
CA 2318818	AA	19990826	CA 1999-2318818	19990217
AU 9930287	A1	19990906	AU 1999-30287	19990217
AU 746294	B2	20020418		
BR 9908119	A	20001024	BR 1999-8119	19990217
EP 1054994	A2	20001129	EP 1999-911678	19990217
EP 1054994	B1	20041117		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO				
TR 200002431	T2	20010122	TR 2000-200002431	19990217
JP 2002504346	T2	20020212	JP 2000-532542	19990217
JP 3681109	B2	20050810		
TR 200101634	T2	20020621	TR 2001-200101634	19990217
NZ 506138	A	20030725	NZ 1999-506138	19990217
EP 1428826	A2	20040616	EP 2004-2632	19990217
EP 1428826	A3	20041027		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
CN 1535971	A	20041013	CN 2004-10034240	19990217
NZ 525622	A	20041029	NZ 1999-525622	19990217
AT 282710	E	20041215	AT 1999-911678	19990217
PT 1054994	T	20050429	PT 1999-911678	19990217
ES 2233028	T3	20050601	ES 1999-911678	19990217
RU 2268306	C2	20060120	RU 2000-124168	19990217
NO 2000004114	A	20001017	NO 2000-4114	20000817
US 6380227	B1	20020430	US 2000-656954	20000907
HK 1034100	A1	20050715	HK 2001-102978	20010425
US 2002165256	A1	20021107	US 2002-59587	20020129
US 6656711	B2	20031202		
US 2003194787	A1	20031016	US 2003-338336	20030108
US 2003220379	A1	20031127	US 2003-459762	20030612
US 2004142990	A1	20040722	US 2004-754661	20040108
JP 2005068156	A2	20050317	JP 2004-287797	20040930
NO 2005002034	A	20001017	NO 2005-2034	20050426

PRIORITY APPLN. INFO.:

CH 1998-396	A	19980219
CH 1998-1007	A	19980505
US 1999-248910	A3	19990212
EP 1999-911678	A3	19990217
JP 2000-532542	A3	19990217
WO 1999-EP1025	W	19990217
US 2000-656954	A1	20000907
US 2002-59587	A3	20020129
US 2003-338336	B1	20030108

AB The invention relates to a process for concentrating epothilones in culture media, a process for the production of epothilones, a process for separating epothilones A and B and a strain obtained by mutagenesis for the production of epothilones, as well as aspects related thereto. Crystal forms of epothilone B are also described.

ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:549398 CAPLUS
DOCUMENT NUMBER: 131:169392
TITLE: Fermentative preparation process for cytostatics and crystal forms thereof
INVENTOR(S): Hofmann, Hans; Mahnke, Marion; Memmert, Klaus; Petersen, Frank; Schupp, Thomas; Kusters, Ernst; Mutz, Michael
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9942602	A2	19990826	WO 1999-EP1025	19990217
WO 9942602	A3	19991125		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6194181	B1	20010227	US 1999-248910	19990212
CA 2318818	AA	19990826	CA 1999-2318818	19990217
AU 9930287	A1	19990906	AU 1999-30287	19990217
AU 746294	B2	20020418		
BR 9908119	A	20001024	BR 1999-8119	19990217
EP 1054994	A2	20001129	EP 1999-911678	19990217
EP 1054994	B1	20041117		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO				
TR 200002431	T2	20010122	TR 2000-200002431	19990217
JP 2002504346	T2	20020212	JP 2000-532542	19990217
JP 3681109	B2	20050810		
TR 200101634	T2	20020621	TR 2001-200101634	19990217
NZ 506138	A	20030725	NZ 1999-506138	19990217
EP 1428826	A2	20040616	EP 2004-2632	19990217
EP 1428826	A3	20041027		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
CN 1535971	A	20041013	CN 2004-10034240	19990217
NZ 525622	A	20041029	NZ 1999-525622	19990217
AT 282710	E	20041215	AT 1999-911678	19990217
PT 1054994	T	20050429	PT 1999-911678	19990217
ES 2233028	T3	20050601	ES 1999-911678	19990217
RU 2268306	C2	20060120	RU 2000-124168	19990217
NO 2000004114	A	20001017	NO 2000-4114	20000817
US 6380227	B1	20020430	US 2000-656954	20000907
HK 1034100	A1	20050715	HK 2001-102978	20010425
US 2002165256	A1	20021107	US 2002-59587	20020129
US 6656711	B2	20031202		
US 2003194787	A1	20031016	US 2003-338336	20030108
US 2003220379	A1	20031127	US 2003-459762	20030612
US 2004142990	A1	20040722	US 2004-754661	20040108
JP 2005068156	A2	20050317	JP 2004-287797	20040930
NO 2005002034	A	20001017	NO 2005-2034	20050426
PRIORITY APPLN. INFO.:			CH 1998-396 A	19980219

CH 1998-1007	A	19980505
US 1999-248910	A3	19990212
EP 1999-911678	A3	19990217
JP 2000-532542	A3	19990217
WO 1999-EP1025	W	19990217
US 2000-656954	A1	20000907
US 2002-59587	A3	20020129
US 2003-338336	B1	20030108

AB The invention relates to a process for concentrating epothilones in culture media, a process for the production of epothilones, a process for separating epothilones A and B and a strain obtained by mutagenesis for the production of epothilones, as well as aspects related thereto. Crystal forms of epothilone B are also described.

L5 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:811346 CAPLUS
DOCUMENT NUMBER: 132:60132
TITLE: Genes for the biosynthesis of epothilones by Sorangium cellulosum
INVENTOR(S): Schupp, Thomas; Ligon, James Madison; Molnar, Istvan; Zirkle, Ross; Gorlach, Jorn; Cyr, Devon
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft mbH
SOURCE: PCT Int. Appl., 174 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966028	A2	19991223	WO 1999-EP4171	19990616
WO 9966028	A3	20000629		
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
NZ 508326	A	20031031	NZ 1998-508326	19980612
CA 2329774	AA	19991223	CA 1999-2329774	19990616
AU 9946116	A1	20000105	AU 1999-46116	19990616
AU 753567	B2	20021024		
BR 9911349	A	20010313	BR 1999-11349	19990616
EP 1088078	A2	20010404	EP 1999-929243	19990616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO				
TR 200003759	T2	20010621	TR 2000-200003759	19990616
JP 2002518004	T2	20020625	JP 2000-554837	19990616
RU 2234532	C2	20040820	RU 2000-131705	19990616
RU 2265054	C2	20051127	RU 2003-130458	19990616
US 6121029	A	20000919	US 1999-335409	19990617
US 6346404	B1	20020212	US 2000-568102	20000510
US 6355457	B1	20020312	US 2000-567969	20000510
US 6355458	B1	20020312	US 2000-568480	20000510
US 6355459	B1	20020312	US 2000-568486	20000510
US 6358719	B1	20020319	US 2000-568472	20000510
US 6383787	B1	20020507	US 2000-567899	20000510
ZA 2000007145	A	20011022	ZA 2000-7145	20001204
NO 2000006195	A	20010216	NO 2000-6195	20001206
US 2002192778	A1	20021219	US 2001-14717	20011113
US 6858404	B2	20050222		
JP 2006061166	A2	20060309	JP 2005-305998	20051020

PRIORITY APPLN. INFO.:

US 1998-155183P	P	19980618
US 1998-99504	A	19980618
US 1998-101631P	P	19980924
US 1999-118906P	P	19990205
JP 2000-554837	A3	19990616
RU 2000-131705	A	19990616
WO 1999-EP4171	W	19990616
US 1999-335409	A3	19990617
US 2000-568472	A1	20000510

AB Nucleic acid mols. are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of epothilone in Sorangium

cellulosum strain 90 (DSM 6773). The gene cluster includes 22 open reading frames, several of which include domains for a given distinct activity of the epothilone synthase, including acyl carrier protein, β-ketosynthase, acyltransferase, β-ketoreductase, dehydratase, enoyl reductase, and thioesterase. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

L5 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:592097 CAPLUS
DOCUMENT NUMBER: 143:103272
TITLE: Therapeutic formulations containing epothilone derivatives
INVENTOR(S): Sherrill, Michael; Johnson, Robert G.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S. Ser. No.683,952.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005148543	A1	20050707	US 2004-962308	20041008
WO 2004032866	A2	20040422	WO 2003-US32055	20031009
WO 2004032866	A3	20040729		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004132692	A1	20040708	US 2003-683952	20031009

PRIORITY APPLN. INFO.:		
US 2003-683952	A2	20031009
WO 2003-US32055	A2	20031009
US 2002-417536P	P	20021009
US 2002-426585P	P	20021114

AB Formulations comprising one or more **epothilones** together with a pharmaceutically acceptable carrier are described. E.g., an **epothilone** D-hydroxypropyl β- **cyclodextrin** lyophylizate was prepared for reconstitution for injections.

L5 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:346870 CAPLUS
DOCUMENT NUMBER: 142:397752
TITLE: Therapeutic formulations containing epothilones
INVENTOR(S): Sherrill, Michael; Johnson, Robert G., Jr.
PATENT ASSIGNEE(S): Kosan Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005034964	A1	20050421	WO 2004-US33339	20041008
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,				

AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

WO 2004032866 A2 20040422 WO 2003-US332055 20031009

WO 2004032866 A3 20040729

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004132692 A1 20040708 US 2003-683952 20031009

PRIORITY APPLN. INFO.: US 2003-683952 A 20031009

WO 2003-US32055 A 20031009

US 2002-417536P P 20021009

US 2002-426585P P 20021114

AB Formulations comprise 1 or more **epothilones** together with a pharmaceutically acceptable carrier. Thus, a combination of 10 mg **epothilone** D and 0.4 g hydroxypropyl-3-**cyclodextrin** were dissolved in 60% tert-butanol-water to make 1 mL of solution A second solution having 10 mg **epothilone** D and 10 mg mannitol dissolved in 60% tert-butanol-water was prepared A third solution of 10 mg **epothilone** D and 10 mg mannitol in 60% tert-butanol-water was also prepared Each of the 3 solns. was freeze-dried to form an excellent cake. The cake containing hydroxypropyl-β- **cyclodextrin** appeared harder and less smooth than the other 2 cakes.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:1066047 CAPLUS

DOCUMENT NUMBER: 142:62404

TITLE: Kinetics and mechanism of degradation of epothilone-D: An experimental anticancer agent

AUTHOR(S): Jumaa, M.; Carlson, B.; Chimilio, L.; Silchenko, S.; Stella, V. J.

CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS, 66047, USA

SOURCE: Journal of Pharmaceutical Sciences (2004), 93(12), 2953-2961

CODEN: JPMSAE; ISSN: 0022-3549

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The objective of this study was to investigate the stability and the degradation pathway of **epothilone**-D (Epo-D), an exptl. anticancer agent. In pH range 4-9, Epo-D displayed pH-independent stability and the highest stability was observed at pH 1.5-2 where its thiazole group is protonated. Increasing the pH >9 or <1.5 resulted in an increase in the degradation rate. Epo-D contains an ester group that can be hydrolyzed. The formation of the hydrolytic product was confirmed by the NMR, fast atom bombardment mass spectroscopy, and liquid chromatog./mass spectroscopy/mass spectroscopy techniques. The largely sigmoidal pH-rate profile is not consistent with the normal pH dependency of ester hydrolysis involving an addition/elimination mechanism. Hence, a hydrolysis mechanism through a carbonium ion was suggested. At pH 4 and 7.4, no buffer catalysis was observed (0.01, 0.02, and 0.05 M buffers) and no significant deuterium kinetic solvent isotope effect was noted. The degradation was very sensitive to changes in the dielec. constant of the solvents as significant

enhancement in the stability was observed in buffer-acetonitrile and 0.1 M (SBE)7m-β- **cyclodextrin** solns. compared with just buffer, suggesting that the rate-determining step in the degradation pathway involved formation of a polar transition state. Mass spectral anal. of the reaction run in 18O water was consistent with incorporation of the 18O in the alc. hydroxyl rather than the carboxylate group. These observations strongly support the carbonium ion mechanism for the hydrolysis of Epo-D in the pH range 4-9. A pKa value of 2.86 for Epo-D was estimated from the fit of the pH-rate profile. This number was confirmed independently by the changes in UV absorbance of Epo-D as a function of pH (pKa 3.1) determined at 25°C and the same ionic strength.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:331933 CAPLUS
DOCUMENT NUMBER: 140:344910
TITLE: Therapeutic formulations containing epothilones for treatment of hyperproliferative diseases
INVENTOR(S): Sherrill, Michael; Johnson, Robert G.
PATENT ASSIGNEE(S): Kosan Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004032866	A2	20040422	WO 2003-US32055	20031009
WO 2004032866	A3	20040729		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1551425	A2	20050713	EP 2003-773227	20031009
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006504743	T2	20060209	JP 2004-543618	20031009
WO 2005034964	A1	20050421	WO 2004-US33339	20041008
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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US 2005148543	A1	20050707	US 2004-962308	20041008

PRIORITY APPLN. INFO.:		
US 2002-417536P	P	20021009
US 2002-426585P	P	20021114
US 2003-683952	A	20031009
WO 2003-US32055	W	20031009

AB Formulations comprising one or more **epothilones** together with a

pharmaceutically acceptable carrier, in particular such pharmaceutical compns. suitable for oral administration of an **epothilone** are described. For example, a combination of 10 mg of **epothilone** D and 0.4 g of hydroxypropyl-β- **cyclodextrin** were dissolved in 60% tert-butanol-water to make 1 mL of solution The solution was freeze-dried and formed an excellent lyophilate cake. The cake appeared harder and less smooth than the one containing mannitol. The **epothilone** D formulation had good oral bioavailability, suggesting that oral administration to cancer patients or patients suffering from other hyperproliferative conditions or diseases is feasible.

L5 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:811346 CAPLUS
DOCUMENT NUMBER: 132:60132
TITLE: Genes for the biosynthesis of epothilones by Sorangium cellulosum
INVENTOR(S): Schupp, Thomas; Ligon, James Madison; Molnar, Istvan; Zirkle, Ross; Gorlach, Jorn; Cyr, Devon
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft mbH
SOURCE: PCT Int. Appl., 174 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966028	A2	19991223	WO 1999-EP4171	19990616
WO 9966028	A3	20000629		
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
NZ 508326	A	20031031	NZ 1998-508326	19980612
CA 2329774	AA	19991223	CA 1999-2329774	19990616
AU 9946116	A1	20000105	AU 1999-46116	19990616
AU 753567	B2	20021024		
BR 9911349	A	20010313	BR 1999-11349	19990616
EP 1088078	A2	20010404	EP 1999-929243	19990616
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TR 200003759	T2	20010621	TR 2000-200003759	19990616
JP 2002518004	T2	20020625	JP 2000-554837	19990616
RU 2234532	C2	20040820	RU 2000-131705	19990616
RU 2265054	C2	20051127	RU 2003-130458	19990616
US 6121029	A	20000919	US 1999-335409	19990617
US 6346404	B1	20020212	US 2000-568102	20000510
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US 6355459	B1	20020312	US 2000-568486	20000510
US 6358719	B1	20020319	US 2000-568472	20000510
US 6383787	B1	20020507	US 2000-567899	20000510
ZA 2000007145	A	20011022	ZA 2000-7145	20001204
NO 2000006195	A	20010216	NO 2000-6195	20001206
US 2002192778	A1	20021219	US 2001-14717	20011113
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PRIORITY APPLN. INFO.:			US 1998-155183P P	19980618

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US 1998-101631P	P	19980924
US 1999-118906P	P	19990205
JP 2000-554837	A3	19990616
RU 2000-131705	A	19990616
WO 1999-EP4171	W	19990616
US 1999-335409	A3	19990617
US 2000-568472	A1	20000510

AB Nucleic acid mols. are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of epothilone in Sorangium cellulosum strain 90 (DSM 6773). The gene cluster includes 22 open reading frames, several of which include domains for a given distinct activity of the epothilone synthase, including acyl carrier protein, β-ketosynthase, acyltransferase, β-ketoreductase, dehydratase, enoyl reductase, and thioesterase. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:549398 CAPLUS
DOCUMENT NUMBER: 131:169392
TITLE: Fermentative preparation process for cytostatics and crystal forms thereof
INVENTOR(S): Hofmann, Hans; Mahnke, Marion; Memmert, Klaus; Petersen, Frank; Schupp, Thomas; Kusters, Ernst; Mutz, Michael
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9942602	A2	19990826	WO 1999-EP1025	19990217
WO 9942602	A3	19991125		
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6194181	B1	20010227	US 1999-248910	19990212
CA 2318818	AA	19990826	CA 1999-2318818	19990217
AU 9930287	A1	19990906	AU 1999-30287	19990217
AU 746294	B2	20020418		
BR 9908119	A	20001024	BR 1999-8119	19990217
EP 1054994	A2	20001129	EP 1999-911678	19990217
EP 1054994	B1	20041117		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO				
TR 200002431	T2	20010122	TR 2000-200002431	19990217
JP 2002504346	T2	20020212	JP 2000-532542	19990217
JP 3681109	B2	20050810		
TR 200101634	T2	20020621	TR 2001-200101634	19990217
NZ 506138	A	20030725	NZ 1999-506138	19990217
EP 1428826	A2	20040616	EP 2004-2632	19990217

EP 1428826	A3	20041027			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY					
CN 1535971	A	20041013	CN 2004-10034240		19990217
NZ 525622	A	20041029	NZ 1999-525622		19990217
AT 282710	E	20041215	AT 1999-911678		19990217
PT 1054994	T	20050429	PT 1999-911678		19990217
ES 2233028	T3	20050601	ES 1999-911678		19990217
RU 2268306	C2	20060120	RU 2000-124168		19990217
NO 2000004114	A	20001017	NO 2000-4114		20000817
US 6380227	B1	20020430	US 2000-656954		20000907
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US 2002165256	A1	20021107	US 2002-59587		20020129
US 6656711	B2	20031202			
US 2003194787	A1	20031016	US 2003-338336		20030108
US 2003220379	A1	20031127	US 2003-459762		20030612
US 2004142990	A1	20040722	US 2004-754661		20040108
JP 2005068156	A2	20050317	JP 2004-287797		20040930
NO 2005002034	A	20001017	NO 2005-2034		20050426
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			CH 1998-1007	A	19980505
			US 1999-248910	A3	19990212
			EP 1999-911678	A3	19990217
			JP 2000-532542	A3	19990217
			WO 1999-EP1025	W	19990217
			US 2000-656954	A1	20000907
			US 2002-59587	A3	20020129
			US 2003-338336	B1	20030108

AB The invention relates to a process for concentrating epothilones in culture media, a process for the production of epothilones, a process for separating epothilones A and B and a strain obtained by mutagenesis for the production of epothilones, as well as aspects related thereto. Crystal forms of epothilone B are also described.

L5 ANSWER 7 OF 7 MEDLINE on STN

ACCESSION NUMBER:	2004551316 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 15459947
TITLE:	Kinetics and mechanism of degradation of epothilone-D: an experimental anticancer agent.
AUTHOR:	Jumaa M; Carlson B; Chimilio L; Silchenko S; Stella V J
CORPORATE SOURCE:	Department of Pharmaceutical Chemistry, University of Kansas, 2095 Constant Avenue, Lawrence, Kansas 66047, USA.
CONTRACT NUMBER:	N01-CM-77017 (NCI) N01-CM27004 (NCI)
SOURCE:	Journal of pharmaceutical sciences, (2004 Dec) Vol. 93, No. 12, pp. 2953-61. Journal code: 2985195R. ISSN: 0022-3549.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200504
ENTRY DATE:	Entered STN: 20041104 Last Updated on STN: 20050413 Entered Medline: 20050412

AB The objective of this study was to investigate the stability and the degradation pathway of **epothilone**-D (Epo-D), an experimental anticancer agent. In pH range 4-9, Epo-D displayed pH-independent stability and the highest stability was observed at pH 1.5-2 where its thiazole group is protonated. Increasing the pH >9 or <1.5 resulted in an increase in the degradation rate. Epo-D contains an ester group that can be hydrolyzed. The formation of the hydrolytic product was confirmed by the nuclear magnetic resonance (NMR), fast atom bombardment mass spectroscopy and liquid chromatography/mass spectroscopy/mass spectroscopy

techniques. The largely sigmoidal pH-rate profile is not consistent with the normal pH dependency of ester hydrolysis involving an addition/elimination mechanism. Hence, a hydrolysis mechanism through a carbonium ion was suggested. At pH 4 and 7.4, no buffer catalysis was observed (0.01, 0.02, and 0.05 M buffers) and no significant deuterium kinetic solvent isotope effect was noted. The degradation was very sensitive to changes in the dielectric constant of the solvents as significant enhancement in the stability was observed in buffer-acetonitrile and 0.1 M (SBE)7m-beta-**cyclodextrin** solutions compared with just buffer, suggesting that the rate-determining step in the degradation pathway involved formation of a polar transition state. Mass spectral analysis of the reaction run in 18O water was consistent with incorporation of the 18O in the alcohol hydroxyl rather than the carboxylate group. These observations strongly support the carbonium ion mechanism for the hydrolysis of Epo-D in the pH range 4-9. A pKa value of 2.86 for Epo-D was estimated from the fit of the pH-rate profile. This number was confirmed independently by the changes in ultraviolet absorbance of Epo-D as a function of pH (pKa 3.1) determined at 25 degrees C and the same ionic strength.

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=> d his

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L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:549398 CAPLUS
DOCUMENT NUMBER: 131:169392
TITLE: Fermentative preparation process for cytostatics and crystal forms thereof
INVENTOR(S): Hofmann, Hans; Mahnke, Marion; Memmert, Klaus; Petersen, Frank; Schupp, Thomas; Kusters, Ernst; Mutz, Michael
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 9942602	A3	19991125		
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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AU 9930287	A1	19990906	AU 1999-30287	19990217
AU 746294	B2	20020418		
BR 9908119	A	20001024	BR 1999-8119	19990217
EP 1054994	A2	20001129	EP 1999-911678	19990217
EP 1054994	B1	20041117		
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JP 2002504346	T2	20020212	JP 2000-532542	19990217
JP 3681109	B2	20050810		
TR 200101634	T2	20020621	TR 2001-200101634	19990217
NZ 506138	A	20030725	NZ 1999-506138	19990217
EP 1428826	A2	20040616	EP 2004-2632	19990217
EP 1428826	A3	20041027		
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RU 2268306	C2	20060120	RU 2000-124168	19990217
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US 6380227	B1	20020430	US 2000-656954	20000907
HK 1034100	A1	20050715	HK 2001-102978	20010425
US 2002165256	A1	20021107	US 2002-59587	20020129
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US 2003194787	A1	20031016	US 2003-338336	20030108
US 2003220379	A1	20031127	US 2003-459762	20030612
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EP 1999-911678	A3	19990217
JP 2000-532542	A3	19990217
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US 2000-656954	A1	20000907
US 2002-59587	A3	20020129
US 2003-338336	B1	20030108

AB The invention relates to a process for concentrating epothilones in culture media, a process for the production of epothilones, a process for separating epothilones A and B and a strain obtained by mutagenesis for the production of epothilones, as well as aspects related thereto. Crystal forms of epothilone B are also described.

L5 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:811346 CAPLUS
DOCUMENT NUMBER: 132:60132
TITLE: Genes for the biosynthesis of epothilones by Sorangium cellulosum
INVENTOR(S): Schupp, Thomas; Ligon, James Madison; Molnar, Istvan; Zirkle, Ross; Gorlach, Jorn; Cyr, Devon
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft mbH
SOURCE: PCT Int. Appl., 174 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9966028	A2	19991223	WO 1999-EP4171		19990616
WO 9966028	A3	20000629			
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CA 2329774	AA	19991223	CA 1999-2329774		19990616
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AU 753567	B2	20021024			
BR 9911349	A	20010313	BR 1999-11349		19990616
EP 1088078	A2	20010404	EP 1999-929243		19990616
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US 2002192778	A1	20021219	US 2001-14717		20011113
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PRIORITY APPLN. INFO.:

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US 1998-99504	A	19980618
US 1998-101631P	P	19980924
US 1999-118906P	P	19990205
JP 2000-554837	A3	19990616
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US 1999-335409	A3	19990617
US 2000-568472	A1	20000510

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cellulosum strain 90 (DSM 6773). The gene cluster includes 22 open reading frames, several of which include domains for a given distinct activity of the epothilone synthase, including acyl carrier protein, β-ketosynthase, acyltransferase, β-ketoreductase, dehydratase, enoyl reductase, and thioesterase. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

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